from the Brown-Pearce tumor, a growth which normally produces metastases, enhanced both the incidence and the development of metastases in this disease, and that the enhancing material from the Bashford tumor which ordinarily does not produce metastases did not cause the occurrence of metastases recognizable in the gross. The enhancing materials derived from two mammalian tumors seemed to conform to type and one at least is limited in its activity.

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## Traumatic Shock in Adrenalectomized Rats.

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It is well known that an adrenalectomized animal is susceptible to a much smaller dose of a poison than a normal animal. The drugs which have been used in this work are many and quite unrelated. They include histamine (Dale[1]), morphine and bacteria (Scott[2]), and many others (Lewis[3]). Wyman and Tum Suden,[4] however, feel that histamine is fatal in small doses because of absence of the medulla and that intraperitoneal injections of epinephrine can protect against fatal doses of histamine. Nevertheless, cortical extracts are much more effective than epinephrine in this rôle (Marmorston-Gottesman and Perla[5]). Likewise cortical extracts are capable of protection in adrenalectomized animals against fatal doses of typhoid vaccine (Scott and Bradford,[6] Perla and Marmorston-Gottesman[5]).

The sensitivity of adrenalectomized animals to histamine seems a very significant relationship inasmuch as many common serious clinical conditions are assumed to be the result of histamine poisoning. It has been generally accepted from the work of Cannon,[7]

[1] Dale, H. H., *Brit. J. Exp. Path.*, 1920, **1**, 103.

[2] Scott, W. J. M., *J. Exp. Med.*, 1923, **38**, 543; 1924, **39**, 457.

[3] Lewis, J. T., *Am. J. Phys.*, 1923, **64**, 506.

[4] Wyman, L. C., Tum Suden, C., *Am. J. Phys.*, 1932, **99**, 285.

[5] Marmorston-Gottesman, J., and Perla, D., PROC. SOC. EXP. BIOL. AND MED., 1931, **28**, 1022.

[6] Scott, W. J., and Bradford, W. L., PROC. SOC. EXP. BIOL. AND MED., 1931, **28**, 428.

[7] Cannon, W. B., *Compte rend. Soc. Biol.*, 1918, **81**, 850.

Bayliss,[8] and Dale and Laidlaw[9] that traumatic shock is the result of absorption of histamine-like substances from injured tissue into the blood giving the typical histamine reaction, fall in blood pressure, asthenia and sub-normal temperature. These symptoms can be explained on the basis of altered capillary permeability, allowing the escape of plasma into the tissues with the subsequent dehydration of blood.

Rats are very resistant to histamine requiring about 800-1000 mg. per kilo to cause death. It is well known, too, that it is impossible to shock a rat by trauma. Many rats in this laboratory have had all their leg muscles crushed and after recovery from ether anesthesia, return to normal activity except for limping. Because of the loss of resistance to histamine by removing the adrenals we wished to see whether there would be an analogous susceptibility to injured tissues.

Young, vigorous, male rats 35-40 days old were bilaterally adrenalectomized. They were allowed 36 hours to recover from the operation. They were, then, anesthetized with ether and their hind leg muscles crushed with long-nosed pliers. Normal rats were treated likewise and other adrenalectomized rats were simply anesthetized.

The controls recovered completely. For some time after the bruising treatment the adrenalectomized animals appeared normal but within an hour they all began to show unmistakable symptoms of shock. They crouched in corners with fur erect, obviously sick. At the end of 2 hours they were in deep shock, cold, cyanotic and very feeble. One rat survived, 7 rats died at the end of 1½, 3, 4. 5, 6, 7, and 12 hours.

The one that survived began to recover after 6 to 7 hours but it was not normal until about 18 hours from the beginning of the experiment.

A second group of adrenalectomized rats were injured similarly, 18 hours after their adrenals had been removed. Some were injected subcutaneously with 5 cc. normal saline at the time of injury and a second 5 cc. two hours later as they lay in shock. The addition of fluids did not prevent the progress of severe shock, but it did prevent death in most cases. Recovery was apparent after 4-5 hours of complete collapse. Seven of the 9 rats which received no fluids died at the end of 2, 2½, 4, 5, 6, 9, and 10 hours. Two sur-

[8] Bayliss, W. M., Oliver Sharpey Lectures, 1918.

[9] Dale, H. H., and Laidlaw, P. P., *J. Phys.*, 1918, **52**, 355.

vived. Of the 9 rats receiving the fluids one died at the end of 10 hours, 8 survived, but eventually they died of adrenal insufficiency about 9 days later.

The work of Cannon and of Bayliss has long been undisputed. Their theory that shock is due to the absorption of histamine is now being questioned. Robinson and Parsons[10] claim that secondary shock can satisfactorily be explained by the loss of blood into the injured tissues. Blalock *et al.*[11] find that enough fluids escape into the injured and neighboring parts to account for the circulatory collapse. In a recent review on the etiology of traumatic shock (Rikstinat[12]), the loss of blood and fluids into the site of injury is the favored theory. We offer in our experiment some facts which require an explanation other than this.

Our normal rats had extensive tissue damage without the formation of shock. If, however, the adrenals were previously removed, trauma to much less tissue was sufficient to produce definite and usually fatal shock. The swelling of the tissues was no greater in the latter group and therefore loss of fluids into injured tissues could not account for this condition. The only conclusion to be drawn is that the dehydration in the adrenalectomized rats was due to loss of fluids into the general body tissues, a typical histamine reaction. We can nicely apply the theory of Cannon, Bayliss and Dale here. The amount of histamine liberated by the trauma was ineffective in normal rats, but was potent in the sensitive adrenalectomized rats.

*Summary.* 1. Adrenalectomized, but not normal rats are sensitive to trauma and usually die from moderate tissue injury. 2. Injection of normal saline is effective in protecting shocked rats from death. 3. The toxemia theory of shock explains this susceptibility of adrenalectomized rats to injury.

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[10] Robinson, W., and Parsons, E., *Arch. Path.*, 1931, **12**, 1.

[11] Blalock, A., *Arch. Surg.*, 1930, **20**, 959; Blalock, A., Beard, J. M., and Johnson, G. S., *J. Am. Med. Assn.*, 1931, **97**, 1794.

[12] Rikstinat, G. J., *Arch. Path.*, 1932, **14**, 378.